General

Guideline Title

KDIGO clinical practice guideline for glomerulonephritis.

Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl. 2012 Jun;2(2):139-274. [765 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions of the strength of recommendation (Level 1, Level 2, or Not Graded), and the quality of the supporting evidence (A-D) are provided at the end of the 'Major Recommendations' field.

Steroid-Sensitive Nephrotic Syndrome in Children (SSNS)

Treatment of the Initial Episode of SSNS

- The Work Group recommends that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (*1B*)
  - The Work Group recommends that oral prednisone be administered as a single daily dose (*1B*) starting at 60 mg/m^2/d or 2 mg/kg/d to a maximum 60 mg/d. (*1D*)
  - The Work Group recommends that daily oral prednisone be given for 4–6 weeks (*1C*) followed by alternate-day medication as a single daily dose starting at 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg on alternate days) (*1D*) and continued for 2–5 months with tapering of the dose. (*1B*)

Treatment of Relapsing SSNS with Corticosteroids

- Corticosteroid therapy for children with infrequent relapses of SSNS:
  - The Work Group suggests that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m^2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (*2D*)
  - The Work Group suggests that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m^2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (*2C*)
- Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS:

- The Work Group suggests that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (*2C*)
- The Work Group suggests that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (*2D*)
- The Work Group suggests that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (*2D*)
- The Work Group suggests that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (*2C*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in randomized controlled trials (RCTs) depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Treatment of FR and SD SSNS with Corticosteroid-Sparing Agents

- The Work Group recommends that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (*1B*)
- The Work Group recommends that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for FR SSNS. (*1B*) The Work Group suggests that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (*2C*)
  - The Work Group suggests that cyclophosphamide (2 mg/kg/d) be given for 8–12 weeks (maximum cumulative dose 168 mg/kg). (*2C*)
  - The Work Group suggests that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (*2D*)
  - The Work Group suggests that chlorambucil (0.1–0.2 mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (*2C*)
  - The Work Group suggests that second courses of alkylating agents not be given. (*2D*)
- The Work Group recommends that levamisole be given as a corticosteroid-sparing agent. (*1B*)
  - The Work Group suggests that levamisole be given at a dose of 2.5 mg/kg on alternate days (*2B*) for at least 12 months (*2C*) as most children will relapse when levamisole is stopped.
- The Work Group recommends that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (*1C*)
  - The Work Group suggests that cyclosporine be administered at a dose of 4–5 mg/kg/d (starting dose) in two divided doses. (*2C*)
  - The Work Group suggests that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (*2D*)
  - Monitor CNI levels during therapy to limit toxicity. (*Not Graded*)
  - The Work Group suggests that CNIs be given for at least 12 months, as most children will relapse when CNIs are stopped. (*2C*)
- The Work Group suggests that mycophenolate mofetil (MMF) be given as a corticosteroid-sparing agent. (*2C*)
  - The Work Group suggests that MMF (starting dose 1200 mg/m^2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (*2C*)
- The Work Group suggests that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (*2C*)
- The Work Group suggests that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*2C*)
- The Work Group recommends that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (*1B*)

Indication for Kidney Biopsy

- Indications for kidney biopsy in children with SSNS are (*Not Graded*):
  - Late failure to respond following initial response to corticosteroids
  - A high index of suspicion for a different underlying pathology
  - Decreasing kidney function in children receiving CNIs

Immunizations in Children with SSNS

- To reduce the risk of serious infections in children with SSNS (*Not Graded*):
  - Give pneumococcal vaccination to the children.
  - Give influenza vaccination annually to the children and their household contacts.
  - Defer vaccination with live vaccines until prednisone dose is below either 1 mg/kg daily (<20 mg/d) or 2 mg/kg on alternate days (<40 mg on alternate days).
  - Live vaccines are contraindicated in children receiving corticosteroid-sparing immunosuppressive agents.

- Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.
- Following close contact with Varicella infection, give nonimmune children on immunosuppressive agents varicella zoster immune globulin, if available.

Steroid-Resistant Nephrotic Syndrome (SRNS) in Children

Evaluation of Children with SRNS

- The Work Group suggests a minimum of 8 weeks treatment with corticosteroids to define steroid resistance. (*2D*)
- The following are required to evaluate the child with SRNS (*Not Graded*):
  - A diagnostic kidney biopsy
  - Evaluation of kidney function by glomerular filtration rate (GFR) or estimated GFR (eGFR)
  - Quantitation of urine protein excretion

Treatment Recommendations for SRNS

- The Work Group recommends using a CNI as initial therapy for children with SRNS. (*1B*)
  - The Work Group suggests that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (*2C*)
  - The Work Group suggests CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (*2C*)
  - The Work Group suggests that low-dose corticosteroid therapy be combined with CNI therapy. (*2D*)
- The Work Group recommends treatment with angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARBs) for children with SRNS. (*1B*)
- In children who fail to achieve remission with CNI therapy:
  - The Work Group suggests that mycophenolate mofetil (*2D*), high-dose corticosteroids (*2D*), or a combination of these agents (*2D*) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.
  - The Work Group suggests that cyclophosphamide not be given to children with SRNS. (*2B*)
- In patients with a relapse of nephrotic syndrome after complete remission, the Work Group suggests that therapy be restarted using any one of the following options: (*2C*)
  - Oral corticosteroids (*2D*)
  - Return to previous successful immunosuppressive agent (*2D*)
  - An alternative immunosuppressive agent to minimize potential cumulative toxicity (*2D*)

Minimal-Change Disease (MCD) in Adults

Treatment of Initial Episode of Adult MCD

- The Work Group recommends that corticosteroids be given for initial treatment of nephrotic syndrome. (*1C*)
- The Work Group suggests prednisone or prednisolone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). (*2C*)
- The Work Group suggests the initial high dose of corticosteroids, if tolerated, be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. (*2C*)
- In patients who remit, the Work Group suggests that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. (*2D*)
- For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis), the Work Group suggests oral cyclophosphamide or CNIs as discussed in frequently relapsing MCD. (*2D*)
- The Work Group suggests using the same initial dose and duration of corticosteroids for infrequent relapses as in the recommendations above. (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

FR/SD MCD

- The Work Group suggests oral cyclophosphamide 2–2.5 mg/kg/d for 8 weeks. (*2C*)
- The Work Group suggests CNI (cyclosporine 3–5 mg/kg/d or tacrolimus 0.05–0.1 mg/kg/d in divided doses) for 1–2 years for FR/SD

MCD patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility. (*2C*)
- The Work Group suggests MMF 500–1000 mg twice daily for 1–2 years for patients who are intolerant of corticosteroids, cyclophosphamide, and CNIs. (*2D*)

Corticosteroid-Resistant MCD

- Re-evaluate patients who are corticosteroid-resistant for other causes of nephrotic syndrome. (*Not Graded*)

Supportive Therapy

- The Work Group suggests that MCD patients who have acute kidney injury (AKI) be treated with renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD. (*2D*)
- The Work Group suggests that, for the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria. (*2D*)

Idiopathic Focal Segmental Glomerulosclerosis in Adults

Initial Evaluation of FSGS

- Undertake thorough evaluation to exclude secondary forms of FSGS. (*Not Graded*)
- Do not routinely perform genetic testing. (*Not Graded*)

Initial Treatment of FSGS

- The Work Group recommends that corticosteroid and immunosuppressive therapy be considered only in idiopathic FSGS associated with clinical features of the nephrotic syndrome. (*1C*)
- The Work Group suggests prednisone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg). (*2C*)
- The Work Group suggests the initial high dose of corticosteroids be given for a minimum of 4 weeks; continue high-dose corticosteroids up to a maximum of 16 weeks, as tolerated, or until complete remission has been achieved, whichever is earlier. (*2D*)
- The Work Group suggests corticosteroids be tapered slowly over a period of 6 months after achieving complete remission. (*2D*)
- The Work Group suggests CNIs be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis). (*2D*)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this section refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

Treatment for Relapse

- The Work Group suggests that a relapse of nephrotic syndrome is treated as per the recommendations for relapsing MCD in adults (see recommendations above). (*2D*)

Treatment for Steroid-Resistant FSGS

- For steroid-resistant FSGS, the Work Group suggests that cyclosporine at 3–5 mg/kg/d in divided doses be given for at least 4–6 months. (*2B*)
- If there is a partial or complete remission, the Work Group suggests continuing cyclosporine treatment for at least 12 months, followed by a slow taper. (*2D*)
- The Work Group suggests that patients with steroid-resistant FSGS, who do not tolerate cyclosporine, be treated with a combination of mycophenolate mofetil and high-dose dexamethasone. (*2C*)

Idiopathic Membranous Nephropathy (IMN)

Evaluation of MN

- Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven membranous nephropathy. (*Not Graded*)

Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents (see the recommendations for children with IMN in the section below).

- The Work Group recommends that initial therapy be started only in patients with nephrotic syndrome AND when at least one of the

following conditions is met:

- Urinary protein excretion persistently exceeds 4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy during an observation period of at least 6 months (*1B*)
- The presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome (*1C*)
- Serum creatinine (SCr) has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m^2 AND this change is not explained by superimposed complications. (*2C*)

- Do not use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (>309 μmol/l) (or an eGFR <30 ml/min per 1.73 m^2) AND reduction of kidney size on ultrasound (e.g., <8 cm in length) OR those with concomitant severe or potentially life-threatening infections. (*Not Graded*)

Initial Therapy of IMN

- The Work Group recommends that initial therapy consist of a 6-month course of alternating monthly cycles of oral and intravenous (i.v.) corticosteroids, and oral alkylating agents (see Table 15 in the original guideline document). (*1B*)
- The Work Group suggests using cyclophosphamide rather than chlorambucil for initial therapy. (*2B*)
- The Work Group recommends patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present (see 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents,' above). (*1C*)
- Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (>15 g/d). (*Not Graded*)
- Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (*Not Graded*)
- The Work Group suggests that continuous daily (noncyclical) use of oral alkylating agents may also be effective, but can be associated with greater risk of toxicity, particularly when administered for >6 months. (*2C*)

Alternative Regimens for the Initial Therapy of IMN: CNI Therapy

- The Work Group recommends that cyclosporine or tacrolimus be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents,') but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen (see Table 18 in the original guideline document for specific recommendations for dosage during therapy). (*1C*)
- The Work Group suggests that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. (*2C*)
- The Work Group suggests that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. (*2C*)
- The Work Group suggests that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (>20%) during therapy. (*Not Graded*) (See Table 18 in the original guideline document for specific CNI-based regimen dosage recommendations.)

Regimens Not Recommended or Suggested for Initial Therapy of IMN

- The Work Group recommends that corticosteroid monotherapy not be used for initial therapy of IMN. (*1B*)
- The Work Group suggests that monotherapy with MMF not be used for initial therapy of IMN. (*2C*)

Treatment of IMN Resistant to Recommended Initial Therapy

- The Work Group suggests that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (*2C*)
- The Work Group suggests that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (*2C*)

Treatment for Relapses of Nephrotic Syndrome in Adults with IMN

- The Work Group suggests that relapses of nephrotic syndrome in IMN be treated by reinstitution of the same therapy that resulted in the initial remission. (*2D*)
- The Work Group suggests that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy (see 'Initial Therapy of IMN,' above), the regimen be repeated only once for treatment of a relapse. (*2B*)

Treatment of IMN in Children

- The Work Group suggests that treatment of IMN in children follows the recommendations for treatment of IMN in adults. (*2C*) (See 'Selection of Adult Patients with IMN to Be Considered for Treatment with Immunosuppressive Agents' and 'Initial Therapy on IMN,' above.)
- The Work Group suggests that no more than one course of the cyclical corticosteroid/alkylating-agent regimen be given in children. (*2D*)

Prophylactic Anticoagulants in IMN

- The Work Group suggests that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (<2.5 g/dl [<25 g/l]) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using oral warfarin. (*2C*)

Idiopathic Membranoproliferative Glomerulonephritis (MPGN)

Evaluation of MPGN

- Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (see Table 20 in the original guideline document). (*Not Graded*)

Treatment of Idiopathic MPGN

- The Work Group suggests that adults or children with presumed idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function receive oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy limited to less than 6 months. (*2D*)

Infection-Related Glomerulonephritis (GN)

- For the following infection-related GN, the Work Group suggests appropriate treatment of the infectious disease and standard approaches to management of the kidney manifestations: (*2D*)
  - Poststreptococcal GN
  - Infective endocarditis-related GN
  - Shunt nephritis

Hepatitis C Virus (HCV) Infection–Related GN

- For HCV-infected patients with CKD Stages 1 or 2 and GN, the Work Group suggests combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*)
  - Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)
- For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, the Work Group suggests monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*)
- For patients with HCV and mixed cryoglobulinemia (immunoglobulin G [IgG]/immunoglobulin M [IgM]) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, the Work Group suggests either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

Hepatitis B Virus (HBV) Infection–Related GN

- The Work Group recommends that patients with HBV infection and GN receive treatment with interferon-α or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (see Table 23 in the original guideline document). (*1C*)
- The Work Group recommends that the dosing of these antiviral agents be adjusted to the degree of kidney function. (*1C*)

Human Immunodeficiency Virus (HIV) Infection–Related Glomerular Disorders

- The Work Group recommends that antiretroviral therapy be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. (*1B*)

Schistosomal, Filarial, and Malarial Nephropathies

- The Work Group suggests that patients with GN and concomitant malarial, schistosomal, or filarial infection be treated with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. (*Not Graded*)

- The Work Group suggests that corticosteroids or immunosuppressive agents not be used for treatment of schistosomal-associated GN, since the GN is believed to be the direct result of infection and the attendant immune response to the organism. (*2D*)
- The Work Group suggests that blood culture for *Salmonella* be considered in all patients with hepatosplenic schistosomiasis who show urinary abnormalities and/or reduced GFR. (*2C*)
    - The Work Group suggests that all patients who show a positive blood culture for *Salmonella* receive anti-*Salmonella* therapy. (*2C*)

Immunoglobulin A Nephropathy (IgAN)

Initial Evaluation Including Assessment of Risk of Progressive Kidney Disease

- Assess all patients with biopsy-proven IgAN for secondary causes of IgAN. (*Not Graded*)
- Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (*Not Graded*)
- Pathological features may be used to assess prognosis. (*Not Graded*)

Antiproteinuric and Antihypertensive Therapy

- The Work Group recommends long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (*1B*)
- The Work Group suggests ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d (in children, between 0.5 to 1 g/d per 1.73 m^2). (*2D*)
- The Work Group suggests the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (*2C*)
- In IgAN, use blood pressure treatment goals of <130/80 mmHg in patients with proteinuria <1 g/d, and <125/75 mmHg when initial proteinuria is >1 g/d (see Chapter 2 in the original guideline document). (*Not Graded*)

Corticosteroids

- The Work Group suggests that patients with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR <50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Immunosuppressive Agents (Cyclophosphamide, Azathioprine, MMF, Cyclosporine)

- The Work Group suggests not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see 'Crescentic IgAN,' below). (*2D*)
- The Work Group suggests not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see 'Atypical Forms of IgAN,' below). (*2C*)
- The Work Group suggests not using MMF in IgAN. (*2C*)

Other Treatments

Fish Oil Treatment

- The Work Group suggests using fish oil in the treatment of IgAN with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (*2D*)

Antiplatelet Agents

- The Work Group suggests not using antiplatelet agents to treat IgAN. (*2C*)

Tonsillectomy

- The Work Group suggests that tonsillectomy not be performed for IgAN. (*2C*)

Atypical Forms of IgAN

MCD with Mesangial IgA Deposits

- The Work Group recommends treatment as for MCD (see 'Minimal-Change Disease in Adults,' above) in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (*2B*)

AKI Associated with Macroscopic Hematuria

- Perform a repeat kidney biopsy in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (*Not Graded*)
- The Work Group suggests general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only acute tubular necrosis (ATN) and intratubular erythrocyte casts. (*2C*)

Crescentic IgAN

- Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. (*Not Graded*)
- The Work Group suggests the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see 'Pauci-Immune Focal and Segmental Necrotizing Glomerulonephritis,' below). (*2D*)

Henoch-Schönlein Purpura (HSP) Nephritis

Treatment of HSP Nephritis in Children

- The Work Group suggests that children with HSP nephritis and persistent proteinuria, >0.5–1 g/d per 1.73 m^2, are treated with ACE-I or ARBs. (*2D*)
- The Work Group suggests that children with persistent proteinuria, >1 g/d per 1.73 m^2, after a trial of ACE-I or ARBs, and GFR >50 ml/min per 1.73 m^2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see 'Immunoglobulin A Nephropathy,' above). (*2D*)

Treatment of Crescentic HSP Nephritis in Children

- The Work Group suggests that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see 'Crescentic IgAN,' above). (*2D*)

Prevention of HSP Nephritis in Children

- The Work Group recommends not using corticosteroids to prevent HSP nephritis. (*1B*)

HSP Nephritis in Adults

- The Work Group suggests that HSP nephritis in adults be treated the same as in children. (*2D*)

Lupus Nephritis (LN)

Class I LN (Minimal-Mesangial LN)

- The Work Group suggests that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (*2D*)

Class II LN (Mesangial-Proliferative LN)

- Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (*2D*)
- The Work Group suggests that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (see 'Minimal-change Disease in Adults,' above). (*2D*)

Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Initial Therapy

- The Work Group recommends initial therapy with corticosteroids (*1A*), combined with either cyclophosphamide (*1B*) or MMF (*1B*).
- The Work Group suggests that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (*2D*)

Class III LN (Focal LN) and Class IV LN (Diffuse LN)—Maintenance Therapy

- The Work Group recommends that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (*1B*)
- The Work Group suggests that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF

and azathioprine. (*2C*)
- The Work Group suggests that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (*2D*)
- If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)
- While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, the Work Group suggests that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

Class V LN (Membranous LN)

- The Work Group recommends that patients with class V LN, normal kidney function, and non–nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)
- The Work Group suggests that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide (*2C*), or CNI (*2C*), or MMF (*2D*), or azathioprine (*2D*).

General Treatment of LN

- The Work Group suggests that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (*2C*)

Class VI LN (Advanced Sclerosis LN)

- The Work Group recommends that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (*2D*)

Relapse of LN

- The Work Group suggests that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (*2B*)
    - If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then the Work Group suggests a non–cyclophosphamide-based initial regimen be used (see Regimen D, Table 28 in the original guideline document). (*2B*)
- Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (*Not Graded*)

Treatment of Resistant Disease

- In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)
- Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see 'Class III LN [Focal LN] and Class IV LN [Diffuse LN]—Initial Therapy,' above). (*Not Graded*)
- The Work Group suggests that nonresponders who have failed more than one of the recommended initial regimens (see 'Class III LN [Focal LN] and Class IV LN [Diffuse LN]—Initial Therapy,' above) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

Systemic Lupus and Thrombotic Microangiopathy

- The Work Group suggests that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2–3). (*2D*)
- The Work Group suggests that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (*2D*)

Systemic Lupus and Pregnancy

- The Work Group suggests that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (*2D*)
- The Work Group recommends that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (*1A*)
- The Work Group suggests that hydroxychloroquine be continued during pregnancy. (*2B*)
- The Work Group recommends that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (*1B*)
- The Work Group recommends that, if LN patients relapse during pregnancy, they receive treatment with corticosteroids and, depending on

the severity of the relapse, azathioprine. (*1B*)
- If pregnant patients are receiving corticosteroids or azathioprine, the Work Group suggests that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (*2D*)
- The Work Group suggests administration of low-dose aspirin during pregnancy to decrease the risk of fetal loss. (*2C*)

LN in Children

- The Work Group suggests that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (*2D*)

Pauci-Immune Focal and Segmental Necrotizing Glomerulonephritis

Initial Treatment of Pauci-Immune Focal and Segmental Necrotizing GN

- The Work Group recommends that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)
- The Work Group recommends that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

Special Patient Populations

- The Work Group recommends the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)
- The Work Group suggests the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)
- The Work Group suggests the addition of plasmapheresis for patients with overlap syndrome of antineutrophil cytoplasmic antibodies (ANCA) vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see 'Treatment of Anti-Glomerular Basement Membrane Antibody Glomerulonephritis,' below) (*2D*)
- The Work Group suggests discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis dependent and who do not have any extrarenal manifestations of disease. (*2C*)

Maintenance Therapy

- The Work Group recommends maintenance therapy in patients who have achieved remission. (*1B*)
- The Work Group suggests continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)
- The Work Group recommends no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

Choice of Agent for Maintenance Therapy

- The Work Group recommends azathioprine 1–2 mg/kg/d orally as maintenance therapy. (*1B*)
- The Work Group suggests that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)
- The Work Group suggests trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)
- The Work Group suggests methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2. (*1C*)
- The Work Group recommends not using etanercept as adjunctive therapy. (*1A*)

Treatment of Relapse

- The Work Group recommends treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see 'Initial Treatment of Pauci-Immune Focal and Segmental Necrotizing GN,' above). (*1C*)
- The Work Group suggests treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

Treatment of Resistant Disease

- In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, the Work Group recommends the addition of rituximab (*1C*), and suggest i.v. immunoglobulin (*2C*) or plasmapheresis (*2D*) as alternatives.

Monitoring

- The Work Group suggests not changing immunosuppression based on changes in ANCA titer alone. (*2D*)

Transplantation

- The Work Group recommends delaying transplantation until patients are in complete extrarenal remission for 12 months. (*1C*)
- The Work Group recommends not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (*1C*)

Treatment of Anti-Glomerular Basement Membrane Antibody Glomerulonephritis (GBM GN)

Treatment of Anti-GBM GN

- The Work Group recommends initiating immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis (see Table 31 in the original guideline document) in all patients with anti-GBM GN except those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage. (*1B*)
- Start treatment for anti-GBM GN without delay once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis (Table 31 in the original guideline document) while waiting for confirmation. (*Not Graded*)
- The Work Group recommends no maintenance immunosuppressive therapy for anti-GBM GN. (*1D*)
- Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months. (*Not Graded*)

Definitions:

Nomenclature and Description for Grading Recommendations

	Implications		
Grade[a]	**Patients**	**Clinicians**	**Policy**
Level 1 'The Work Group recommends'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'The Work Group suggests'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

[a]The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Clinical Algorithm(s)

A management algorithm for patients with acute kidney injury (AKI) associated with macroscopic hematuria is provided in the original guideline

document.

Scope

Disease/Condition(s)

Glomerulonephritis (GN):

- Steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS)
- Minimal-change disease (MCD) and idiopathic focal segmental glomerulosclerosis (FSGS)
- Idiopathic membranous nephropathy (IMN)
- Idiopathic membranoproliferative GN
- GN associated with infections
- Immunoglobulin A (IgA) nephropathy and Henoch-Schönlein purpura (HSP) nephritis
- Lupus nephritis (LN)
- Renal vasculitis
- Anti-glomerular basement membrane (anti-GBM) GN

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Internal Medicine

Nephrology

Pathology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To provide recommendations for the treatment of patients already diagnosed with glomerulonephritis
- To improve patient care by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice

Target Population

Adults and children already diagnosed with glomerulonephritis (GN)

Interventions and Practices Considered

Evaluation

1. Kidney biopsy in children with steroid-sensitive nephrotic syndrome (SSNS) and patients with idiopathic membranous nephropathy (IMN)
2. Evaluation to define steroid resistance in children with steroid-resistant nephrotic syndrome (SRNS) (kidney biopsy, glomerular filtration rate [GFR], estimated GFR, urine protein excretion)
3. Evaluation to exclude secondary forms of focal segmental glomerulosclerosis (FSGS) in adults
4. Genetic testing for FSGS (not recommended routinely)
5. Evaluation to exclude secondary causes of IMN
6. Selection of patients for treatment with immunosuppressive agents (values for urinary protein excretion, serum creatinine, estimated GFR)
7. Evaluation of idiopathic membranoproliferative glomerulonephritis (MPGN) patients for underlying diseases
8. Initial evaluation of immunoglobulin A nephropathy (IgAN), including assessment of risk of progressive kidney disease
9. Repeat kidney biopsy in patients with lupus nephritis

Management/Treatment

1. Corticosteroid therapy (prednisone or prednisolone)
2. Corticosteroid-sparing agents (cyclophosphamide, chlorambucil, levamisole, calcineurin inhibitors [CNI] [cyclosporine, tacrolimus], mycophenolate mofetil [MMF], rituximab, mizoribine and azathioprine)
3. Immunization (avoiding live vaccines in immunosuppressed child with SSNS)
4. Antiproteinuric and antihypertensive therapy (angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin-receptor blocker [ARB])
5. Combination therapies
6. Supportive therapy (renal replacement therapy) in minimal-change disease (MCD)
7. High-dose dexamethasone for steroid-resistant FSGS in those who do not tolerate cyclosporine
8. Prophylactic anticoagulant therapy in IMN
9. Appropriate treatment of underlying infection for patients with infection-related glomerulonephritis (GN)
10. Antiviral treatment using pegylated interferon and ribavirin for hepatitis C-related GN
11. Treatment with interferon-α or nucleoside analogues for hepatitis B-related GN
12. Antiretroviral therapy for human immunodeficiency virus (HIV)-related GN
13. Alternative treatments for IgAN: fish oil treatment, antiplatelet agents (not recommended), tonsillectomy (not recommended)
14. Treatment of lupus nephritis by class—initial and maintenance therapy
15. Hydroxychloroquine for all classes of lupus nephritis
16. Treatment of systemic lupus and thrombotic microangiopathy (anticoagulation, plasma exchange)
17. Plasmapheresis in special populations with Pauci-immune focal and segmental necrotizing GN
18. Etanercept as adjunctive therapy for Pauci-immune focal and segmental necrotizing GN (not recommended)
19. Monitoring immunosuppressive therapy in patients with Pauci-immune focal and segmental necrotizing GN
20. Delaying transplantation until complete remission of Pauci-immune focal and segmental necrotizing GN is achieved
21. Deferring kidney transplantation until anti-GBM antibodies have been undetectable for a minimum of 6 months
22. Treatment of relapsed or resistant disease
23. Treatment of special populations (children, pregnant women)

Major Outcomes Considered

- Changes in proteinuria
- Glomerular filtration rate
- Serum creatinine increases
- Complete or partial remission
- Relapse rates
- Progression of renal disease

- End-stage renal disease
- Death/mortality/survival
- Quality of life
- Protocol-driven additional treatment of glomerulonephritis
- Incidence of adverse drug effects

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Searches and Article Selection

Searches were conducted in MEDLINE and Cochrane through January 20, 2011. All searches were also supplemented by articles identified by Work Group members through November 2011. For detailed search strategies, please see the Online Appendix 1 (see the 'Availability of Companion Documents' field).

Search results were screened by the Evidence Review Team (ERT) for relevance using predefined eligibility criteria, described below. For questions related to treatment, the systematic search aimed to identify randomized controlled trials (RCTs) as described in Table 32 in the original guideline document. For some topics, randomized comparative trials were also reviewed, in addition to RCTs, to strengthen the evidence base.

For most topics, the minimum sample size was >10. For minimal-change disease (MCD) and focal segmental glomerulosclerosis (FSGS), because of sparse data, smaller studies were included.

For most topics, the minimum duration of follow-up of 6 months was chosen based on clinical reasoning. For the treatments of interest, the proposed effects on patient important clinical outcomes require long-term exposure and, typically, would not be expected to become evident before several months of follow-up.

In addition, a search was conducted for data on predictors of kidney failure, kidney function, and remission. Only associations from multivariable regression analyses were considered. These 'predictor studies' were not graded for quality. For these topics, the ERT completed its search in October 5, 2009 and did not update the search.

Included were studies of all patients with glomerular diseases, excluding those with diabetic nephropathy, thrombotic microangiopathy, amyloidosis, Alport's and other hereditary glomerular diseases, paraproteinemia, and recurrence of glomerulonephritis (GN) following kidney transplantation.

Interventions of interest included all treatments for GN, including drugs, herbs, dietary supplements, tonsillectomy, infection prophylaxis, and postdiagnosis tests to determine treatment.

A list of pertinent, published systematic reviews relevant to GN guidelines was generated, organized by topic, and reviewed with the Work Group. If an existing systematic review adequately addressed a question of interest as determined by the Work Group, this was used instead of a *de novo* systematic review by the ERT. These systematic reviews were then used as the starting points for building the evidence base and supplemented with articles from the ERT's own searches. If these reviews were deemed to adequately address topics of interest (even if only selected outcomes were reviewed), *de novo* searches on these topics were limited to the time period since the end of literature search within the systematic reviews.

Editorials, letters, stand-alone abstracts, unpublished reports, and articles published in non–peer-reviewed journals were excluded. The Work Group also decided to exclude publications from journal supplements.

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE and various Cochrane databases were the

only databases searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group. Not all topics and subtopics covered by these guidelines could be systematically reviewed. Decisions to restrict the topics were made to focus the systematic reviews on those topics where existing evidence was thought to be likely to provide support for the guidelines. Although nonrandomized studies were reviewed, the majority of the ERT and Work Group resources were devoted to review of the randomized trials, since these were deemed to be most likely to provide data to support level 1 recommendations with very high- or high- (A or B) quality evidence. Where randomized trials were lacking, it was deemed to be sufficiently unlikely that studies previously unknown to the Work Group would result in higher-quality level 1 recommendations.

Number of Source Documents

Table 33 in the original guideline document summarizes the numbers of abstracts screened, articles retrieved, studies data extracted, and studies included in summary tables.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) System for Grading Quality of Evidence for an Outcome

Step 1: Starting Grade for Quality of Evidence Based on Study Design	
Randomized trials	High
Observational study	Low
Any other evidence	Very low
Step 2: Reduce Grade	
Study quality	-1 level if serious limitations -2 levels if very serious limitations
Consistency	-1 level if important inconsistency
Directness	-1 level if some uncertainty -2 levels if major uncertainty
Other	-1 level if sparse or imprecise data -1 level if high probability of reporting bias
Step 3: Raise Grade	
Strength of association	+1 level if strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity
Other	+1 level if evidence of a dose–response gradient +1 level if all residual plausible confounders would have reduced the observed effect
Final Grade for Quality of Evidence and Definition	
High	Further research is unlikely to change confidence in the estimate of the effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
Very low	Any estimate of effect is very uncertain

[a]Strong evidence of association is defined as 'significant relative risk (RR) of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.

[b]Very strong evidence of association is defined as 'significant RR of >5 (<0.2)' based on direct evidence with no major threats to validity.

[c]Sparse if there is only one study or if total N <100. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range <0.5 to >2.0.

Modified with permission from Uhlig et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 70: 2058–2065; and Atkins et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328:1490.

Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

The Evidence Review Team (ERT) designed data-extraction forms to tabulate information on various aspects of the primary studies. Data fields for all topics included study setting, patient demographics, eligibility criteria, type of glomerulonephritis (GN), numbers of subjects randomized, study design, study funding source, descriptions of interventions (or predictors), description of outcomes, statistical methods used, results, quality of outcomes (as described below), limitations to generalizability, and free-text fields for comments and assessment of biases.

Summary Tables

Summary tables were developed to tabulate the data from studies pertinent to each question of intervention. Each summary table contains a brief description of the outcome, baseline characteristics of the population, intervention, comparator results, and methodological quality of each outcome. Baseline characteristics include a description of the study size, country of residence, and baseline kidney function and proteinuria. Intervention and concomitant therapies, and the results, were all captured. The studies were listed by outcome within the table, based on the hierarchy of important outcomes (see Table 34 in the original guideline document). Categorical and continuous outcomes were summarized in separate sets of tables. Work Group members were asked to proof all data in summary tables on randomized controlled trials (RCTs) and non-RCTs. Separate sets of summary tables were created for predictor studies. Summary tables are available at www.kdigo.org/clinical_practice_guidelines/GN.php .

Evidence Profiles

Evidence profiles were constructed by the ERT and reviewed and confirmed with the Work Group members. These profiles serve to make transparent to the reader the thinking process of the Work Group in systematically combining evidence and judgments. Each evidence profile was reviewed by Work Group members. Decisions were based on facts and findings from the primary studies listed in corresponding summary tables, as well as selected existing systematic reviews, and judgments of the Work Group. Judgments about the quality, consistency, and directness of evidence were often complex, as were judgments about the importance of an outcome or the summary of effects sizes. The evidence profiles provided a structured transparent approach to grading, rather than a rigorous method of quantitatively summing up grades. Evidence profiles were constructed for research questions addressed by at least two studies. When the body of evidence for a particular comparison of interest consisted of only one study, either an RCT or a systematic review, the summary table provides the final level of synthesis.

Grading the Quality of Evidence

A structured approach, based on Grading Recommendations Assessment, Development and Evaluation (GRADE) and facilitated by the use of

evidence profiles, was used in order to grade the quality of the overall evidence. For each topic, the discussion on grading of the quality of the evidence was led by the ERT. The 'quality of a body of evidence' refers to the extent to which the confidence in an estimate of effect is sufficient to support a particular recommendation.

Grading the Quality of Evidence for Each Outcome

Following the GRADE method, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized based on study design. For questions of interventions, the initial quality grade was 'High' when the body of evidence consisted of RCTs. In theory, the initial grade would have been 'Low' if the evidence consisted of observational studies or 'Very Low' if it consisted of studies of other study designs; however, the quality of bodies of evidence was formally determined only for topics where we performed systematic reviews of RCTs. The grade for the quality of evidence for each intervention/outcome pair was decreased if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or CI spanning a range <0.5 to >2.0) or sparse (only one study or total N<100), or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention/outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low', or 'Very Low' (see the 'Rating Scheme for the Strength of the Evidence' field). The quality of grading for topics relying on systematic reviews are based on quality items recorded in the systematic review.

Grading the Overall Quality of Evidence

The quality of the overall body of evidence was then determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome, weighting critical outcomes more than high or moderate. The resulting four final categories for the quality of overall evidence were: 'A', 'B', 'C' or 'D' (see the 'Rating Scheme for the Strength of the Evidence' field). This evidence grade is indicated within each recommendation.

See the original guideline document for additional discussion of evaluation of individual studies and assessment of net health benefit across all important clinical outcomes.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overview of Process

The Work Group, Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chairs, the Evidence Review Team (ERT), and National Kidney Foundation (NKF) support staff met for three 3-day meetings for training in the guideline development process, topic discussion, and consensus development.

Creation of Groups

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled the Work Group to be responsible for the development of the guidelines. The Work Group included individuals with expertise in adult and pediatric nephrology, epidemiology, and kidney pathology. For support in evidence review, expertise in methods, and guideline development, the NKF contracted with the ERT based at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA. The ERT consisted of physician-methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

Systematic Review: General Process

The first task of the Work Group was to define the overall topics and goals for the guideline. The Work Group Co-Chairs drafted a preliminary list of topics. The Work Group identified the key clinical questions and triaged topics for systematic review and narrative review. The Work Group and ERT further developed and refined each systematic review topic, specified screening criteria, literature search strategies, and data extraction forms.

The ERT performed literature searches, and conducted abstract and article screening. The ERT also coordinated the methodological and analytic processes of the report. In addition, it defined and standardized the methodology in relation to these searches and data extraction, and produced summaries of the evidence. Throughout the project, the ERT offered suggestions for guideline development, led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and recommendations, and consensus development. With input from the Work Group, the ERT finalized eligible studies, performed all data extraction, and summarized data into summary tables. They also created preliminary evidence profiles, which were completed by the Work Group members. The Work Group members reviewed all included articles, data extraction forms, and summary tables for accuracy and completeness. The Work Group took the primary role of writing the recommendations and rationale statements, and retained final responsibility for the content of the recommendation statements and the accompanying narrative.

For questions of treatments in glomerulonephritis (GN), systematic reviews of the eligible randomized controlled trials (RCTs) were undertaken (see Table 32 in the original guideline document). For these topics, the ERT created detailed data-extraction forms and extracted information on baseline data for the populations, interventions, study design, results, and provided an assessment of quality of study and outcomes. The ERT then tabulated studies in summary tables, and assigned grades for the quality of the evidence in consultation with the Work Group.

Refinement of Topics

At the first 3-day meeting, Work Group members added comments to the scope-of-work document as prepared by the Work Group Chairs and ERT, until the initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group aimed to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed. The major topic areas of interest for the care of GN included immunoglobulin A nephropathy (IgAN), lupus and vasculitis, minimal-change disease (MCD) and focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), and infection.

At the initiation of the guideline development process, it was agreed that these guidelines would focus on patients who have GN. Thus, all topics, systematic reviews, and study eligibility criteria were restricted to patients with a biopsy-proven diagnosis of GN, with exceptions for diseases that do not require biopsy confirmation.

Based on the list of topics, the Work Group and ERT developed a list of specific research questions for which systematic review would be performed. For each systematic review topic, the Work Group Co-Chairs and the ERT formulated well-defined systematic review research questions using a well-established system. For each question, explicit criteria were agreed on for the population, intervention or predictor, comparator, outcomes of interest, and study design features. A list of outcomes of interest was generated.

The Work Group and the ERT agreed upon specific outcomes of interest: all-cause mortality, end-stage renal disease (ESRD), disease remission, relapse, proteinuria, kidney function, and adverse events. ESRD and mortality were ranked as being of critical importance. The Work Group ranked patient-centered clinical outcomes (such as death, ESRD, remission and categorical proteinuria and kidney function changes) as more important than intermediate outcomes (such as continuous outcomes of proteinuria and kidney function). Categorical outcomes are those that describe when a patient moves from one health state (e.g., macroalbuminuria) to another (e.g., no albuminuria). Continuous outcomes would be evaluations of the laboratory values alone (e.g., change in proteinuria in mg/dl). The outcomes were further categorized as being of critical, high, or moderate clinical importance to patients with GN. In general, eligibility criteria were determined based on clinical value, relevance to the guidelines and clinical practice, determination whether a set of studies would affect recommendations or the strength of evidence, and practical issues, such as available time and resources.

Grading the Strength of the Recommendations

The strength of a recommendation is graded as Level 1 or Level 2. The 'Rating Scheme for the Strength of the Recommendations' field shows the Kidney Disease: Improving Global Outcomes (KDIGO) nomenclature for grading the strength of a recommendation, and the implications of each level for patients, clinicians, and policy-makers. Recommendations can be for or against doing something. Table 40 in the original guideline document shows that the strength of a recommendation is determined not just by the quality of the evidence, but also by other—often complex—judgments regarding the size of the net medical benefit, values, and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Ungraded Statements

This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; it is not sufficiently specific to allow application of evidence to the issue and, therefore, it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, and the option of an ungraded statement for general guidance, was adopted by the KDIGO Board in December 2008. The Work Group took the primary role of writing the recommendations and rationale statements, and retained final responsibility for the content of the guideline statements and the accompanying narrative. The evidence review team (ERT) reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Rating Scheme for the Strength of the Recommendations

Nomenclature and Description for Grading Recommendations

	Implications		
Grade[a]	**Patients**	**Clinicians**	**Policy**
Level 1 'The Work Group recommends'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'The Work Group suggests'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

[a]The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Review of the Guideline Development Process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria, the Conference on Guideline Standardization (COGS) checklist, and the Institute of Medicine's recent *Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust*. Online Appendices 2 and 3 (see the 'Availability of Companion Documents' field) show the COGS criteria that correspond to the AGREE checklist and the Institute of Medicine standards, and how each one of them is addressed in this guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the 'Major Recommendations' field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Safe and appropriate management of patients with glomerular disease

Potential Harms

- The potential adverse effects of immunosuppressive therapy must always be discussed with the patient and family before treatment is initiated. The risks of treatment with many of the agents are significant and may have a substantial latent period (e.g., cyclophosphamide). A balance must be struck between the potential risks of immunosuppressive treatment for glomerulonephritis and the seriousness of the patient's condition. It is sometimes difficult to reconcile the immediate risks of immunosuppression, in the otherwise clinically well patient, vs. the potential for progression to end-stage renal disease (ESRD). However, given that advanced chronic kidney disease (CKD)—and, particularly, ESRD—is associated with a significant shortening of life expectancy even with dialysis or transplantation, the balancing of risks and benefits over time must be considered. The physician must be aware of this conundrum and where the evidence for treatment is weak (but potentially life-altering) and the risk for harm strong, a full disclosure is mandatory. Individual patient perceptions of the acceptability of any adverse effect may strongly influence the decision (e.g., the possibility of hirsutism with cyclosporine therapy may be perceived as less tolerable in a young female than in an older male). What might be seen as an acceptable trade-off by the physician may not be viewed similarly by the patient, leading to an issue over compliance with therapy.
- Limiting the long-term adverse effects of treatment is an important objective. Children with frequently relapsing (FR) or steroid-dependent steroid-sensitive nephrotic syndrome (SD SSNS) require prolonged corticosteroid therapy, which is associated with significant adverse effects, including impaired linear growth, behavioral changes, obesity, Cushing's syndrome, hypertension, ophthalmological disorders, impaired glucose tolerance, and reduced bone mineral density. Adverse effects may persist into adult life in young people, who continue to relapse after puberty. To reduce the risk of corticosteroid related adverse effects, children with FR or SD SSNS may require other agents, including alkylating agents (cyclophosphamide, chlorambucil) and calcineurin inhibitors (CNI) (cyclosporine, tacrolimus). Adverse effects of these agents include increased risk of infection and reduced fertility (alkylating agents) and kidney dysfunction and hypertension (CNI).
- The principal side-effects of cyclosporine are kidney dysfunction, hypertension, gum hypertrophy, and hypertrichosis. Hypertension and kidney dysfunction are reported in 5%–10% of children. Hypertrichosis and gum hypertrophy develop in 70% and 30%, respectively, in children treated with cyclosporine for more than 1 year. Tacrolimus also causes kidney dysfunction and hypertension, but significantly less hypertrichosis; tacrolimus-associated diabetes mellitus has been described in children with nephrotic syndrome. In children receiving cyclosporine for 12 months or more, tubulointerstitial lesions on kidney biopsy are reported in 30%–40% of cases. This increases to 80% after 4 or more years of treatment. Cyclosporine-associated arteriopathy is uncommon.
- Rituximab caused acute reactions, such as fever, vomiting and diarrhea, skin rash, and bronchospasm in about one-third of patients in one series. Other reported serious side effects include *Pneumocystis jiroveci* pneumonia and pulmonary fibrosis.
- Adverse effects of levamisole are uncommon and minor, with mild leucopenia and gastrointestinal upsets described. Rare cases of cutaneous vasculitis have been described with levamisole therapy.
- Adverse effects associated with cyclical corticosteroid/alkylating-agent regimen include: enhanced risk of opportunistic infection, reactivation of viral hepatitis, alopecia, gonadal damage (aspermatogenesis, ovulation failure), hemorrhagic cystitis (cyclophosphamide only), neoplasia, myelodysplastic syndrome, acute myelogenous leukemia, transitional cell carcinoma of the bladder, ureter or pelvis, and toxic hepatitis.
- The adverse effects of alkylating-cytotoxic agents are substantial, and include gonadal toxicity, bladder carcinoma, bone marrow hypoplasia, leukemogenesis, and serious opportunistic infections.
- Adverse events including serious infections and deaths have been associated with mycophenolate.
- Ribavirin dose needs to be titrated according to patient tolerance; caution is advised for patients with clearance <50 ml/min which may require substantially reduced dosage.
- Nephrotoxicity of some of the nucleoside analogues (adefovir and tenofovir) can be of concern.
- A study in 80 children with newly diagnosed immunoglobulin A nephropathy (IgAN) compared the effects of the combination of prednisolone, azathioprine, warfarin, and dipyridamole with those of prednisolone alone. Some side-effects were observed including leucopenia, glaucoma, and aseptic necrosis.
- Patients on hydroxychloroquine should have yearly eye examinations for retinal toxicity, especially after 5 years of continuous use.
- Continued maintenance therapy for Pauci-immune focal and segmental necrotizing glomerulonephritis is associated with the risks of immunosuppression, bone marrow suppression (leucopenia, anemia, thrombocytopenia), and possibly increased risk of cancer, notably skin cancer.

Contraindications

Contraindications

- Relative contraindications to high-dose corticosteroids included uncontrolled diabetes, psychiatric conditions, and severe osteoporosis.
- Live vaccines (measles, mumps, rubella, varicella, rotavirus, yellow fever) are contraindicated while on immunosuppressive or cytotoxic agents and should be deferred until prednisone dose is <20 mg/d and/or immunosuppressive agents have been stopped for at least 1–3 months.
- Contraindications to prophylactic anticoagulation are: an uncooperative patient; a bleeding disorder; prior gastrointestinal bleeding; a central nervous lesion prone to hemorrhage (brain tumor, aneurysms); or a genetic abnormality influencing warfarin metabolism or efficacy.
- Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in idiopathic membranous nephropathy (IMN) include:
  - Untreated infection (human immunodeficiency virus [HIV], hepatitis B and C, tuberculosis, fungal infection, etc.)
  - Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.
  - Urinary retention
  - Inability to comply with monitoring
  - Pre-existing leukopenia (<4000 leukocytes/mm^3)
  - Serum creatinine >3.5 mg/dl (>309 mmol/l)

Qualifying Statements

Qualifying Statements

- This Clinical Practice Guideline document is based upon systematic literature searches last conducted in January 2011, supplemented with additional evidence through November 2011. It is designed to provide information and assist decision-making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.
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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl. 2012 Jun;2(2):139-274. [765 references]

Adaptation

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Financial Disclosures/Conflicts of Interest

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is printed in the Biographic and Disclosure Information section of the original guideline document and is on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies of the guideline: Available from the Kidney Disease: Improving Global Outcomes (KDIGO) Web site .

Availability of Companion Documents

The following are available:

- KDIGO clinical practice guideline for glomerulonephritis. Online appendices 1-3. New York: Kidney Disease: Improving Global Outcomes; 2012 May. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the Kidney Disease: Improving Global Outcomes (KDIGO) Web site .
- KDIGO clinical practice guideline for glomerulonephritis. Online supplementary tables. New York: Kidney Disease: Improving Global Outcomes; 2012 May. 144 p. Electronic copies: Available in PDF from the KDIGO Web site .
- Methods for development of KDIGO clinical practice guidelines. Electronic copies: Available from the KDIGO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 26, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

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